



RESEARCH ARTICLE

Clinico-Demographic Profile and Outcomes of COVID-19 Patients Presenting with Acute Ischemic Stroke Admitted at Tondo Medical Center

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Chapter I

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a newly discovered coronavirus that came from Coronavirus family that causes Corona Virus Disease 2019 (COVID-19 Disease). This virus was first documented in December 2019, where it was identified as the cause of a disease outbreak in Wuhan, China that spread worldwide and became pandemic. To date, globally, over 30 million confirmed cases of COVID-19 have been reported.

The virus spreads primarily through droplets. Direct person-to-person contact is the primary means of transmission and via indirect contact, by touching infected objects or surfaces and then touching their eyes, noses or mouths before cleaning their hands. People infected with SARS-CoV-2 Virus will mostly experience mild to moderate respiratory illness and will recover without requiring special treatment. However older people, and those with underlying medical problems specifically those with chronic respiratory disease such as Bronchial asthma, Chronic Obstructive Pulmonary Disease (COPD), Cardiovascular Diseases, Diabetes, Autoimmune diseases and cancer are more likely to develop serious illness. COVID-19 disease not only affects respiratory system but can also impair other systems such as cardiovascular, gastrointestinal, urinary, reproductive and nervous system.

Symptoms of coronavirus affecting the nervous system include but not limited to headache, dizziness, appetite, loss of sense of smell and taste and acute cerebrovascular disease (Ischemic and Hemorrhagic Stroke). Patients infected with SARS-CoV-2 are at risk for acute cerebrovascular disease due to hypercoagulation, blood stasis, and endothelial damage causing thrombosis and the risk of stroke may vary according to the severity of COVID-19. The number of incidences of Acute Ischemic Stroke (AIS) associated with COVID-19 is higher compared, with the incidence of intracranial hemorrhage. Ischemic stroke may present with non-focal deficits, including encephalopathy, and may also involve multiple vascular territories; thus, the clinical signs and symptoms may be different for every patient affected by COVID-19 disease and AIS. This research will be conducted study and discuss the profiles of patients affected by COVID-19 disease and Acute Ischemic Stroke admitted at Tondo Medical Center.

Significance of the study

COVID-19 disease became a pandemic and greatly affected the world. Since the onset of COVID-19 disease outbreak in the country, there are few data about COVID-19 and its correlation with Acute Ischemic Stroke (AIS). Since our center has noticed few numbers of COVID-19 patients presenting with acute cerebral infarct, it is therefore important that this study be conducted that aims to obtain information about COVID-19 disease and its relation to Ischemic Stroke.



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The results of this study will add to the pool of data about COVID-19 infection and its varied manifestation.

General objective

To determine the demographic profile and outcomes of COVID 19 patients who presented with acute ischemic stroke at Tondo Medical Center from April 2020 to January 2021.

Specific objectives

1. To determine the clinical and laboratory parameters on admission of AIS patients with COVID-19 Disease that includes:

- Systolic Blood Pressure
- Diastolic Blood Pressure
- Neurologic Presentation
- Blood Chemistry
- Creatinine;
- Liver enzymes (Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST));
- Electrolytes (Sodium, Potassium, Chloride)
- Lactate Dehydrogenase (LDH);
- D-Dimer;
- C-Reactive Protein Quantitative (CRP);
- Serum Ferritin;
- Prothrombin Time (PT), Partial Prothrombin Time (PTT);
- 12 Lead Electrocardiogram;
- Chest X-Ray (Posterior-Anterior View)
- Plain Cranial Computed Tomography Scan (CT-Scan), specifically the number of territories involved

2. To determine clinical outcomes of COVID and acute ischemic infarct. in terms of:

1. Mortality
2. Intensive Care Unit (ICU) admission and Length of ICU stay
3. Length of total hospital stay.

Chapter II

Related Literature and Studies

In Late 2019, COVID-19 disease caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified causing global outbreak in less than 6 months. To date, there have been 36,996,501 confirmed cases of COVID-19, including 1,069,476 deaths reported according to World Health Organization (WHO).

Despite its common presentation as respiratory distress, patients with COVID-19 have also shown

neurological manifestation especially stroke. The Brain is the potential target to COVID-19, just as the lungs, due to expression of angiotensin-converting enzyme (ACE 2) receptors on the glial cells and neurons of the central nervous system.

Poya Fatehi, et al. [1], studied 5 patients were at Tohid Hospital, Sanandaj, Iran. Three patients were male and two were female. The youngest patient was 20-years-old and the oldest was 55-years-old. Fever, chills, muscular pain, cough, and tachypnea were present in all patients. RBC was observed in all patients at a low level. Plain Cranial CT scans of all patients showed abnormal findings in different areas of the brain. These cases indicate that COVID-19 may damage blood vessels in the brain and lead to stroke.

International Journal of Stroke 2020, Vol 15 (6) NP13-NP14, discussed the increasing reported cases of Neurological complications, in particular ischemic strokes, associated with Coronavirus Disease 2019. The journal studied 22 cases of ischemic stroke in patients with polymerase chain reaction-confirmed COVID-19 in three tertiary hospitals in Dubai, UAE. Most patients were young males, and two-thirds had one or more vascular comorbid conditions. All patients had large territory infarctions, with most having evidence of vessel occlusion on Computerized Tomography (CT) angiogram. Seven patients had free-floating thrombi, one in the aortic arch and others in the carotid arteries detected on CT angiogram. Only two patients had evidence of atherosclerotic disease, and one had a potential cardiac source of embolism. Stroke was the presenting symptom for 18 patients (81.8%); however, 12 of these had respiratory symptoms and/or chest X-ray abnormalities that antedated the stroke symptoms by 1 to 7 days. Four patients had been admitted with pneumonia and neurological deficits developed on days 4, 5, 20 and 21, respectively. Modest elevation of D-dimer and ferritin was found in 81.8% and 58.8% patients, respectively, at the time of their stroke. Similarly, very mild increase of prothrombin time (PT; mean 15.4 s (SD 0.9)) was seen in 10 patients only. The study concluded that majority of our patients presented with stroke symptoms as first evidence of their COVID-19 infection, and the stroke mechanism was predominantly large artery.

Another journal reported by International Journal of Stroke 2020 Vol 15 (6), NP13- NP14, was done at Guglielmo da Saliceto Hospital in Piacenza, one of the outbreak epicenters in Italy. Out of the 19 Strokes occurring in COVID-19-positive patients, admitted from 21 February to 28 April, Two cases (10.5%) were hemorrhagic and 17 (89.5%) ischemic. Mean age was 76.05 years (SD 8.83), 52.6% were male, mean National Institute of Health Stroke Scale (NIHSS) was 9.79 (SD 6.78). Stroke incidence among COVID-19 inpatients was 2.2%. Among the 19 cases, the risk factors were: Diabetes 10.5%, hypertension 84.2%, and atrial fibrillation 31.6%.

Fifteen patients had stroke onset during COVID-19; in four, it preceded COVID-19 diagnosis with a mean delay of 2.5 days (SD 1.0). Ischemic stroke etiologies were large artery atherosclerosis in four cases, cardio-embolism in five, small vessel disease in two, and undetermined in six, of which two were Embolic stroke of undetermined source (ESUS).

P. Belani, et al. (August 2020) is the first study to link COVID 19 Infection and acute ischemic stroke. The study concluded the mean age for cases and controls was 65.5 6 15.3 years and 68.8 6 13.2 years, respectively. Of patients with acute ischemic stroke, 46.3% had COVID-19 infection compared with 18.3% of controls ($P = 0.001$). After adjusting for age, sex, and risk factors, COVID-19 infection had a significant independent association with acute ischemic stroke compared with control subjects (OR, 3.9; 95% CI, 1.7-8.9; $P = 0.001$). However this study suggests that attempts should also be made to see whether the association holds true for large vessel and small-vessel strokes. Patients with COVID-19 should be evaluated early for acute neurologic changes, and timely workup should be performed in patients suspected of having stroke to reduce morbidity and mortality.

In a study done by Adnan I, et al. [2] published in American Heart Association (March 2021), an analysis of 27 676 patients was done and revealed that total of 103 (1.3%) patients developed acute ischemic stroke among 8163 patients with COVID-19. The study also revealed that those patients with existing co morbidities specifically those patients with hypertension, diabetes, hyperlipidemia, atrial fibrillation, and congestive heart failure were significantly higher among those with acute ischemic stroke. Also, Acute ischemic stroke was associated with discharge to destination other than home or death (relative risk, 2.1 [95% CI, 1.6-2.4]; $P < 0.0001$) after adjusting for potential confounders. A total of 199 (1.0%) patients developed acute ischemic stroke among 19 513 patients without COVID-19. Among all ischemic stroke patients, COVID-19 was associated with discharge to destination other than home or death (relative risk, 1.2 [95% CI, 1.0-1.3]; $P = 0.03$) after adjusting for potential confounders. The study concludes that Acute ischemic stroke was infrequent in patients with COVID-19 and usually occurs in the presence of other cardiovascular risk factors. The risk of discharge to destination other than home or death increased 2-fold with occurrence of acute ischemic stroke in patients with COVID-19.

Study done by Ademola S. Ojo, et al. [3] concluded that Acute ischemic strokes are complications of COVID-19 with coagulopathy, endothelial dysfunction, cardio-embolism, and direct viral-mediated neuronal injury as possible underlying causes. The study observed that older patients who presented with severe disease are at a higher risk of this complication, but large-vessel occlusion is being commonly reported in younger patients.

George Ntaios, et al. [4], study findings suggest that COVID-19 associated ischemic strokes are more severe with worse functional outcome and higher mortality than non-COVID-19 ischemic strokes and association between these two disease (COVID-19 and severe stroke) highlights the urgent need for studies aiming to uncover the underlying mechanisms and is relevant for prehospital stroke awareness and in-hospital acute stroke pathways during the current and future pandemics, since severe strokes have typically poor prognosis and can potentially be treated with recanalization techniques.

Chapter III

Methodology

Research design

This investigation determines the correlation between Laboratory Parameters and clinical outcome of patients with COVID-19 Infection and Ischemic Stroke at Tondo Medical Center. In this regard, the researcher employed the Retrospective Research Design.

Population

This study included all admitted patients who are RTPCR swab test positive with presenting signs and symptoms of acute ischemic stroke admitted at the Department of Internal Medicine from April 2020 to January 2021.

Inclusion criteria

1. Adult patients (> 19-years-old) admitted due to AIS
2. COVID-19 confirmed infection using RTPCR
3. Complete data on medical charts

Exclusion criteria

1. Previous Ischemic stroke
2. Ischemic stroke developing during admission

Data collection

A review of patient's records was done after securing approval from the Hospital Research Ethics Committee (REC) and was tabulated using Excel format. Only the previously indicated data was gathered, sorted and treated as approved by the IRB. All information printed on paper was destroyed using paper shredders and computerized data will be deleted one year after the completion of the research.

Data analysis

Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables, median and inter quartile range for non-normally distributed continuous variables and mean

and SD for normally distributed continuous variables. Independent Sample T-test, Mann-Whitney U and Fisher's exact/Chi-square test was used to determine the difference of mean, rank, and frequency, respectively, between alive and expired patients. All statistical tests were two tailed tests. Shapiro-Wilk was used to test the normality of the continuous variables. Missing variables was either replaced nor estimated. Null hypotheses at 0.05 α -level of significance were rejected. STATA 13.1 was used for data analysis.

Ethical consideration

This study is a retrospective review of cases of patients with COVID-19 Disease who presented with AIS admitted at Tondo Medical Center admitted from April 2020 to January 2021. Medical charts are the primary source of data. There is no direct patient contact during the conduct of this study and it is not feasible to contact each patient to obtain informed consent.

To safeguard the privacy and confidentiality of

data, patients' identity and identifying information was excluded from the data collection tool. In its place, numerical codes will be used. The data collected was stored in a computer with password only the primary investigator knows. The investigator and Research Committee will only have the access to the records and will not be disclosed to anyone.

The researcher further declares that there had been no conflict of interest as she conducts this investigation. No commercial or external sources of funds and no sponsorship or solicitation was done.

Chapter IV

Results

Between April 2020 and January 2021, there were at total of 55 cases admitted who presented with Acute Ischemic Stroke and COVID-19 disease in Tondo Medical Center. Of these, nineteen (19) of them have passed the inclusion criteria of this study ([Table 1](#)).

Table 1: Demographic and clinical profile of the patients.

	Total (n = 19)			P-value
Frequency (%); Mean \pm SD; Median (IQR)				
Age	66.68 \pm 8.56	73.33 \pm 6.03	65.44 \pm 8.52	0.148
Sex				0.058
Male	11 (57.89)	0	11 (68.75)	
Female	8 (42.10)	3 (100)	5 (31.25)	
SBP	150 \pm 35.43	123.33 \pm 49	155 \pm 31.83	0.161
DBP	87.37 \pm 17.27	73.33 \pm 23.09	90 \pm 15.49	0.128
Neurologic Presentation				
Altered Mental Status	4 (21.05)	1 (33.33)	3 (18.75)	0.530
Sensory Deficit	4 (21.05)	1 (33.33)	3 (18.75)	0.530
Motor Deficit	17 (89.47)	2 (66.67)	15 (93.75)	0.298
Blood chemistry				
Creatinine	81.8 (73.5-130.3)	149.5 (130-393)	79.77 (71-94)	0.019
SGPT	15.03 (11.4-20.4)	17.79 (11-30.6)	14.98 (11.51-20)	0.655
SGOT	20.36 (15.6-26.1)	20.54 (12-34.7)	20.33 (15.8-26)	1.000
Na	138 (134-142)	133 (125.3-135)	139.45 (136-142)	0.034
K	3.87 (3.54-4.16)	3.82 (3.29-7.7)	3.90 (3.62-4.13)	0.823
CL	106 (102-110)	103 (94.8-113)	106.6 (103-110)	0.655
LDH	119.5 (94-267)	92.73 (83.2-335)	142.7 (104-217)	0.654
D-dimer	0.67 (0.44-1.54)	1.99 (1.54-4)	0.59 (0.4-1.07)	0.019
CRP	12 (6-54.5)	285.9 (30-294)	9 (4.9-37.5)	0.025
Ferritin	461 (254-808)	571.7 (461-891)	370.3 (245-721)	0.371
PT	11.8 (10.5-13)	12.7 (11.8-15)	11.5 (10.45-12.8)	0.198
PTT	27 (24.5-31.2)	27.2 (21.3-33)	26.5 (24.6-30.9)	0.911
12 LEAD ECG	14 (73.68)	2 (66.67)	12 (75)	1.000
Normal Sinus Rhythm				
Chest X-ray (PN)	11 (57.89)	2 (66.67)	9 (56.25)	1.000

Official cranial CT scan No. of territories involved				1.000
1	9 (47.37)	1 (33.33)	8 (50)	
2 or more	10 (52.63)	2 (66.67)	8 (50)	
In-hospital outcome				
Length of hospital stay	12.47 ± 4.93	7.33 ± 2.31	13.44 ± 4.70	0.045
ICU admission	4 (21.02)	3 (100)	1 (6.25)	0.004

Subjects

The mean age of the subjects is 66.68 ± 8.56 years-old ranging from 49 to 80-years-old. Majority of them being male (11, 57.89%).

The average systolic and diastolic blood pressure of patients are 150 (range: 90 to 220 mmHg) and 87.37 (range: 60-120 mmHg), respectively. Most of them having either stage 1 (3, 15.7%) or stage 2 hypertension (12, 63.15%), according to the 2017 ACC/AHA Blood Pressure Category.

Most of the subjects presented with Motor Deficit (17, 89.47%) and the rest presented with Altered Mental status (4, 21.05%) and Sensory deficit (4, 21.05%).

Clinical outcome

Of the subjects of the study, 16 (84.2%) were discharged after admission, while 3 (15.78%) died. The average length of hospital stay is 12.47 ± 4.93 days. The average hospital stay of those who were discharged and died was 13.44 days and 7.33 days respectively. Among the subjects, 4 (21%) were admitted at ICU, 3 among those admitted at ICU died and 1 (6.25%) was discharged.

Clinical characteristics were compared based on patients' outcome discharged or died. There is no significant difference on patient's mean Age, Gender, SBP, DBP, SGPT, SGOT, Potassium, Chloride, LDH, PT and PTT were not significantly different based on outcomes.

Presence of Pneumonia was also examined, and results showed that there were 11 patients (57.89%) who presented with Pneumonia upon admission. Among these patients, 9 (56.25%) were discharged and only 2 (18.18%) died. There is higher median Sodium at 139.45 to alive patients compared to expired patients at 133. Alive patients also had higher median D-dimer at 1.99 compared to expired patients at 0.59, and higher median CRP at 285 compared to expired patients at 9. Expired patients were noted to have lower mean length of hospital stay measured in days at 7.33 ± 2.31 compared to alive patients at 13.44 ± 4.70 and higher median Creatinine at 149.5 compared to alive patients at 79.77.

Chapter V

Discussion

Thromboembolic events are being reported to be increased in patients with coronavirus disease 2019

(COVID-19) and Cerebrovascular accidents (CVA) particularly Ischemic stroke are amongst the common neurologic complications in this disease. In the study, it shows that the mean of the subjects is 66-years-old with majority of them being male. This is not surprising given that ischemic stroke is also very common population-wide, and more common among males than females. The average systolic and diastolic blood pressure of patients are also elevated in the study, 150 mmHg and 87 mmHg respectively, and classified as Hypertension Stage 2 based on the 2017 ACC/AHA Blood Pressure Category. Motor Deficit was as frequent as 89.47% as presenting symptom of the stroke, and the rest presented with Altered Mental status and Sensory deficit. This depends on the number of territories involved in the brain. It is noted also in this study that most of the patients in had multiple territories affected by stroke based on the Plain Cranial CT scan imaging reflecting large artery ischemia. Motor deficit, despite being the most frequent presenting symptom was not associated with increased mortality.

Majority also of the subjects had Pneumonia on Chest X-ray upon admission. It appears that COVID-19 disease still primarily involves the Pulmonary System.

D-dimer, Ferritin and CRP were notably elevated indicating a high inflammatory state and abnormalities with the coagulation cascade, respectively, that plays a role in the pathophysiology of stroke in the setting of COVID-19 infection. Other Laboratory abnormalities noted on the study were low serum sodium and elevated Creatinine levels which could reflect multi organ system involvement of disease caused by the COVID-19 disease.

Of the subjects of the study, majority were discharged after admission. The average length of hospital stay is 13 days that depends mostly on the severity of the COVID 19 infection. Moreover, majority also of the patients who were initially admitted at ICU case were also discharged [5-13].

Chapter VI

Conclusion

Elevation in serum markers of inflammation (CRP, D-Dimer and LDH) were noted on this study that possibly contributed the occurrence of ischemic stroke among them. However, on this study it is not associated with higher mortality.

Higher values of clinical results for serum creatinine, and low values for serum Sodium was found to be more associated to mortality. This only implies that patients with COVID-19 and acute ischemic stroke have a much higher occurrence of multisystem involvement including acute kidney injury.

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